

Immunological Mechanisms Operative in Allergen-Specific Immunotherapy

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Key Words

Type I allergy · Immunotherapy, specific · Th1 · Th2 · Immune deviation · Tolerance

Abstract

Specific immunotherapy (SIT) is the practice of administering increasing doses of allergen extracts to selected subjects suffering from IgE-mediated hypersensitivity, with the ultimate aim of ameliorating the symptoms associated with exposure to the causative allergen. The process is often called hyposensitization or desensitization because one consequence of the treatment is a reduction in sensitivity of the target organ after challenge with the relevant allergen. SIT has been practiced as treatment of type I allergy caused by inhalant allergens and *Hymenoptera* venoms for more than 80 years on an empirical basis. Today, numerous double-blind, placebo-controlled studies prove the therapeutic effect of SIT. However, the immunological mechanisms underlying successful specific immunotherapy have still not been completely elucidated. This review focuses on recent attempts to characterize the immunological events associated with SIT.

Clinical Efficacy of Specific Immunotherapy

Conventional specific immunotherapy (SIT), i.e. the subcutaneous injection of allergen extracts, is a curative treatment for special forms of IgE-mediated allergies. It is particularly effective in patients suffering from rhinitis and asthma elicited by pollens [1–6], house dust mite allergy [6–10] and *Hymenoptera* venom [11, 12]. SIT is the only treatment that may affect the natural course of allergic diseases, as it may prevent the onset of new sensitizations and influences the natural course of the disease, e.g. it prevents the development of asthma in patients with allergic rhinitis [13, 14]. Therefore, SIT can also be regarded as a preventive treatment. It can be concluded that allergen extracts for SIT represent immune modifiers. Standardized allergen extracts have been designated ‘vaccines’ in the recently published WHO Position Paper on allergen immunotherapy [15]. As mentioned above, conventional SIT is performed by subcutaneously injecting allergen extracts. Alternative routes (oral, sublingual, nasal) of the vaccine administration have been tested. The results of clinical studies evaluating the efficacy of these therapeutic strategies varied considerably, possibly due to different protocols concerning duration of treatment, administered doses and methodological problems. However, from the literature it seems that the nasal as well as the sublingual route could represent efficient – and most importantly – safe ways of administering SIT vaccines [16–19].

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Immunological Changes during Immunotherapy

Changes in the Humoral Immune Responses to the Allergen

Allergen-specific serum IgE levels do not decrease significantly during SIT. On the contrary, during the initial dose increase phase a boost leading to increased levels of specific IgE can be observed [20, 21]. On the other hand, allergen-specific IgG antibodies, mainly of the IgG4 isotype, increase constantly during the treatment period [21, 22]. IgG4 antibodies do not mediate antibody-dependent effector mechanisms (e.g. complement activation). The antibodies are obviously necessary to clear the large amounts of protein from the organism. The tremendous rise of specific IgG had previously been interpreted as the production of so-called 'blocking antibodies', which bind to and thereby neutralize the allergen before it has the possibility to interact with cell-bound IgE antibodies [23, 24]. Today, the increase of IgG is considered an epiphenomenon: identical rises in IgG can be observed in SIT responders and nonresponders. Follow-up of successfully treated patients indicated that the allergen-specific IgG titers decrease and return to levels similar to the state before SIT, while the therapy success still persists. Furthermore, rush immunotherapy, a treatment schedule where maintenance doses can be reached within very short time periods (hours), is clinically effective before IgG levels start to rise [25–28].

Changes in the Cellular Immune Response to the Allergen

The synthesis of IgE antibodies is regulated by cytokines produced by a special population of T lymphocytes, so-called T helper 2 (Th2) cells, which are characterized by the secretion of interleukin 4 (IL-4), an inducer of IgE synthesis, and IL-5 [recruits and activates eosinophil granulocytes; 29–31]. Th2 cells represent an extremity in a broad spectrum of CD4⁺ Th cells with overlapping functions. The other extreme is represented by a cell designated Th1. This type of CD4⁺ lymphocytes is associated with cell-mediated inflammatory pathologies such as delayed-type hypersensitivity reactions. The cytokine profile of Th1 lymphocytes is characterized by the production of large amounts of interferon- γ (IFN- γ), IL-2 and tumor necrosis factors. Th1 cytokines, especially IFN- γ , function as natural antagonists for Th2 activities. It was tempting to speculate that SIT would act by modulating the allergic immune response at the level of allergen-specific Th cells, and thereby lead to an improvement in allergy symptoms. Indeed, Secrist et al. [32] demonstrated for the first time that the quantity of IL-4 produced by allergen-specific memory CD4⁺ T cells from allergic individuals in vitro could be considerably reduced

by in vivo treatment with allergen. Moreover, it was demonstrated that the reduction of IL-4 levels was inversely related to the length of time on immunotherapy. Allergen-induced IFN- γ and IL-2 production were not significantly influenced by SIT. One problem concerning this investigation is that the immunological changes were not monitored longitudinally, as SIT-treated patients were compared to a nontreated control group [32]. With respect to IL-4, the data were confirmed by other investigations, mainly performed in bee venom-allergic individuals. However, immunotherapy with bee venom resulted not only in a decrease of Th2 but also in an increase of Th1 cytokines in allergen-stimulated T cell cultures [33–35]. Jutel and colleagues [34] demonstrated that during rush immunotherapy a decrease of phospholipase A2(PLA)-induced IL-4 and IL-5 production in vitro could be observed already after hours. Subsequently, these cytokines decreased constantly during the whole treatment period. At the same time, PLA-induced IFN- γ secretion continuously rose. These events were accompanied by a constant decrease in proliferative responses of PLA-stimulated cells in vitro [33]. One single-year follow-up study chronologically evaluated the immunological changes induced by conventional SIT with grass pollen extract. Before SIT, the majority of allergen-specific Th clones from allergic patients revealed a typical Th2-like pattern of cytokine production in response to allergen stimulation. Th cultures displayed an altered IL-4/IFN- γ ratio after the initial dose increase phase and after 1 year of SIT. Again, simultaneously, proliferative responses to a grass pollen allergen were significantly reduced [21]. In another series of studies, the influence of SIT on the cellular infiltration (late-phase responses) in mucosa and skin was analyzed. The SIT-generated suppression of the late nasal responses occurred together with a decreased number of eosinophils in the nose and the skin. Moreover, signs for Th1 activation could be detected, as the number of cells expressing mRNA for IFN- γ was increased in biopsy specimens after local provocation [36, 37]. The immunological mechanism underlying this immune deviation is seemingly the induction of IL-12 production, as the SIT-effected inhibition of allergen-induced late skin responses was accompanied by increases of IL-12 mRNA in local macrophages [38]. One possible interpretation of this finding is that under circumstances where high amounts of allergens are present in the system – which is the case during SIT – not only highly specialized antigen-presenting cells, such as specific B cells and dendritic cells, but also other antigen-presenting cells – e.g. macrophages – take up and present allergen peptides to T cells. Consequently, considerable amounts of IL-12 are secreted into the environment where the antigen pre-

sensation occurs leading to a shift from Th2 to a more Th1-like response of specific CD4⁺ cells [39–41]. High concentrations of antigen will moreover lead to a high density of TCR ligations, a situation that also favors the production of Th1 cytokines [42].

Lymphoproliferative responses to allergen are markedly reduced after SIT [21, 33, 43]. Moreover, according to Akdis et al. [44] the levels of allergen-induced T cell-derived cytokines – IL-4, IL-5, IL-13 and IFN- γ – decrease during the course of SIT. This effect is specific as responses to control antigens are unchanged. This state of antigen-specific unresponsiveness is commonly referred to as immunological tolerance. Allergen-stimulation of lymphocyte cultures prepared from the peripheral blood of SIT-treated patients led to a decrease in the production of all Th cytokines with the exception of IL-10. This cytokine was produced and secreted in higher amounts as a result of SIT [45]. Suppressed antigen-specific proliferative and cytokine responses in vitro could be reconstituted by inactivation of IL-10 by neutralizing antibodies, indicating the immunomodulation by this cytokine. IL-10 is a regulatory cytokine (also referred to as ‘cytokine synthesis inhibitory factor’) which has been attributed to the Th2 subpopulation in mice, but is produced by Th1- and Th2-like cells in humans [46–49]. There are indications that increased production of IL-10 accounts for the tolerance induced by SIT [44, 45], as this cytokine is known to induce tolerance when administered together with antigen in the mouse system [50]. Recently a regulatory T cell subset producing high levels of IL-10, suppressing antigen-specific immune responses has been identified in mice and humans [51]. Both reports identifying IL-10 as crucial factor in the development to tolerance in Th2 lymphocytes are results from studies applying bee venom SIT. As type I allergy to insect venom does not belong to the cluster of atopic allergies it remains to be shown that the same mechanism is operative during successful pollen or house dust mite SIT.

Conclusion

Reviewing the recent literature on immunological mechanisms in SIT discrepancies concerning the behavior of certain cytokines can be observed. This may partly be due to the different scientific approaches used to investigate the problem. However, summing up, two major components seem to be involved in the mechanism underlying clinically successful SIT: (1) immune deviation, i.e. a shift from a Th2- to a Th1-biased immune response to the allergen; this effect is possibly mediated by IL-12, the strongest inducer

of Th1 responses known, and (2) immunological tolerance obviously induced by the immunosuppressive cytokine IL-10. Together these events lead to a marked reduction of Th2 lymphocyte-derived cytokines, which are involved in the production of IgE antibodies, the priming of mast cells and the recruitment as well as activation of typical allergic inflammatory cells, mainly eosinophil granulocytes. The consequences at the effector cell level have been observed already years ago [52–56]. Further clarification is needed concerning the question of why the levels of allergen-specific IgE antibodies remain elevated though the responsible stimuli have obviously been eliminated. One possible answer would be that once ‘IgE-committed’, B lymphocytes hardly respond to cytokine stimuli [57].

The knowledge of immunological mechanisms operative in SIT and of cytokines mediating these functions will certainly lead to new therapy forms of SIT. Prototypes of allergen preparations with suitable characteristics have been generated. For example, allergens with reduced anaphylactogenic potential but high T cell antigenicity could be used to modulate the allergic immune response at the level of T helper lymphocytes, but without the risk of anaphylactic side effects [58–60]. Moreover, it is conceivable that substances known to induce Th1-biased immune responses [like viral or bacterial proteins, 61, or immunostimulatory oligonucleotides, 62] could be administered as adjuvants together with allergens. The danger of inducing pathologies associated with Th1 reactivity has to be evaluated. However, steering against predominant Th2 immunity by using Th1 inducers should direct the atopic immune system towards a physiological condition, which is obviously similar to a Th0 response. In our opinion, therapy approaches directly interfering with cytokine functions should only be taken into consideration when the respective networks are understood in detail. The time point of this is presently not foreseeable.

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